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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/765,026	01/13/97	BARKATS M	ST9405I-US

EXAMINER	
GUZO,D	
ART UNIT	**PAPER NUMBER**
1636	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/765,026	Barkats et al.
Examiner	**Group Art Unit**
David Guzo	1636

☒ Responsive to communication(s) filed on *Aug 6, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *47 and 61-82* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *47 and 61-82* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47, 61-65, 67 and 69-81 are rejected under 35 USC 103(a) as being unpatentable over Yu et al. in view of Coyle et al. and Greenberger.

Applicants claim a method for treating diseases such as ALS, Parkinson's disease (PD), hypertension, etc., wherein said diseases are characterized by an excess of free radicals, said

method comprising administering to patients a replication defective adenovirus encoding a superoxide dismutase operatively linked to a promoter enabling expression in a target cell.

Yu et al. (U.S. Patent 5,506,133, issued 4/9/96, filed 4/11/94, see whole document, particularly Column 2, lines 15-25; Column 6, lines 1-13 and Columns 9-10) recites the use of a human superoxide dismutase (SOD-4) to treat human diseases involving excess free radicals (i.e. diseases characterized by inflammation, etc.). Yu et al. discloses that adenoviral vectors can be used to express the SOD gene in target cells *in vivo*. Yu et al. also recites that defective human CuZnSOD has been linked to familial ALS. Yu et al. does not teach the specifics of generating adenoviral vectors capable of expressing SOD genes and does not provide a review of the roles of different SODs in reducing the levels of free radicals in humans.

Coyle et al. (Science, Vol. 262, 29 Oct. 1993, pp. 689-695, see whole article, particularly pp. 689-690 and 694) recites the role played by free radicals in diseases such as ALS, PD, etc., reviews the well known roles of the different forms of SODs in reducing the levels of free radicals and the possible correlation between reduction or lose of CuZnSOD activity with diseases such as ALS in humans.

Greenberger (U.S. Patent 5,599,712, See whole document, particularly Figs. 3a-3b, the paragraph bridging Columns 5-6, Columns 7-8, paragraph bridging Columns 11-12, Columns 13 and 16) teaches the specifics of the generation of replication defective adenoviral vectors capable of expressing human SODs (i.e. MnSOD or CuZnSOD, etc. derived from genomic or cDNA sources) wherein the SOD gene is under control of a viral (i.e. the adenoviral MLP) promoter,

human cells which are infected with said vectors and pharmaceutical compositions comprising said vectors. The vectors serve to reduce the level of free radicals in target cells.

The basic concept of the claimed invention is disclosed by Yu et al. in that Yu et al. discloses use of adenoviral vectors to deliver a human SOD gene to target tissues so as to alleviate disease conditions associated with excess free radicals. The secondary references, Coyle et al. and Greenberger et al., simply provide teachings on the specifics of generating adenoviral vectors (these procedures are well known in the art) and provide a review of the link between free radicals and diseases in humans.

The ordinary skilled artisan, seeking to treat diseases which are characterized by an excess of free radicals would have been motivated to combine the teachings of Yu et al. on the use of adenoviral vectors comprising a human SOD gene (SOD-4) to deliver an SOD gene to target tissues so as to alleviate disease conditions which involve excess free radicals (i.e. diseases involving inflammation, oxidative stress, etc.) with the teachings of Coyle et al. on the role of excess free radicals in disease conditions such as PD and ALS and the possible correlation between reducing said levels of excess free radicals and alleviating disease conditions combined with the teachings of Greenberger on the generation of recombinant adenoviral vectors designed for the delivery of SODs to target cells wherein said adenoviral vectors are designed to reduce the levels of free radicals and thereby reduce the levels of cell damage due to said free radicals so as to use said adenoviral vectors to treat diseases characterized by an excess of free radicals. It would have been obvious for the skilled artisan to do this because Yu et al. specifically teaches

that adenoviral vectors (which can be made by the methods disclosed by Greenberger et al.) can be used to deliver an SOD gene to target cells for the express purpose of alleviating diseases marked by an excess of free radicals and because Coyle et al. indicates that a reduction in the levels of free radicals can alleviate some human diseases characterized by excess free radical levels. Given the teachings of the cited prior art references, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 66 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. in view of Coyle et al., Greenberger and further in view of Engelhardt et al.

Yu et al. and Coyle et al. are cited as in the above 35 USC 103(a) rejection.

Greenberger (U.S. Patent 5,599,712), is cited as in the above 103(a) rejection. Greenberger does not recite the generation of adenoviral vectors containing non-functional E2, E4, etc. genes.

Engelhardt et al. (PNAS, Vol. 91, June 1994, pp. 6196-6200, see whole article, particularly the Abstract and last three paragraphs of the Discussion) teaches the use of adenoviral vectors containing a non-functional E2 gene. It is noted that PNAS Volume 91 was received in the U.S. Patent Office Biotechnology Library on June 27, 1994. Coyle et al. and Greenberger teach the basic aspects of the claimed invention absent the use of adenoviral vectors comprising inactivated or nonfunctional additional adenoviral genes such as the E2 gene. Since Engelhardt et al. teaches the desirability of using adenoviral vectors wherein the E2 gene is non-functional (i.e. said vectors

result in improved transgene persistence and reduced inflammatory responses), it must be considered that the ordinary skilled artisan, seeking to generate an adenoviral vector for the expression of SOD, would have been motivated to use an adenoviral vector wherein the E2 gene is non-functional for the express, art recognized, desirability of using these vectors (i.e. generating an adenoviral vector construct desirable for use in gene therapy). It would have been obvious for the ordinary skilled artisan to use an adenoviral construct lacking a functional E2 gene because of the desirability (as disclosed by Engelhardt et al.) of using such a vector for gene therapy. Given the teachings of the cited prior art references and absent evidence to the contrary, it must be considered that the claimed invention would have been *prima facie* obvious to the ordinary skilled artisan and that said artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Coyle et al. in view of Greenberger and Le Gal La Salle et al.

Yu et al., Coyle et al. and Greenberger are applied as in the above 35 USC 103 rejections. Yu et al. Coyle et al. and Greenberger do not teach the use of the RSV-LTR promoter to drive expression of a heterologous gene in an adenovirus vector.

Le Gal La Salle et al. (Science, Vol. 259, 12 Feb. 1993, pp. 988-990, see whole article, particularly p. 988) recites the use of the RSV-LTR promoter in the context of driving expression of heterologous genes in recombinant adenoviruses.

Yu et al., Coyle et al. and Greenberger teach the essential aspects of the invention with the exception of using the RSV-LTR promoter to drive expression of the SOD gene. However, Le Gal La Salle et al. teach the use of the RSV-LTR promoter to drive expression of heterologous genes in a recombinant adenovirus expression vector. The ordinary skilled artisan, therefore, would have been motivated to use the RSV-LTR promoter for the express purpose of driving expression of the heterologous gene (i.e. the SOD gene) since Le Gal La Salle et al. specifically recites using the RSV-LTR promoter to drive expression of a heterologous gene in the context of a replication defective recombinant adenovirus vector. It would have been obvious for the ordinary skilled artisan to use this promoter because it is a well known promoter which has been used in the prior art (Le Gal La Salle et al.) to drive expression of heterologous genes in the context of a recombinant replication defective adenovirus vector. Given the teachings of the cited prior art, it must be considered that the ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

In view of the new ground of rejection, applicants arguments, filed in the Appeal Brief of 8/6/99, are moot. However, in the Brief, applicants' take issue with the teachings of Coyle et al. concerning the role free radicals play in certain neurodegenerative diseases. Applicants assert that Coyle is at best equivocal about treating neurodegenerative diseases by reducing free radicals in target cells.

In response, it is noted that free radicals are involved in a variety of diseases, including certain neurodegenerative diseases, and that defects in SOD function are linked to neurodegenerative diseases such as ALS (see Yu et al., column 2). Indeed, applicants themselves in the instant specification admit that "Thus it is **nowadays recognized** that these free radicals are involved in atherosclerosis, cardiovascular diseases, cirrhosis of the liver, diabetes, cataract formation, in a certain number of neurological diseases including Parkinson's disease and cerebral ischemia, in trisomy 21, and also in the aging process." (instant specification, p. 2). Therefore, since applicants admit that it was recognized that free radicals are involved in a variety of diseases and since a defective CuZnSOD has been linked to ALS in humans and since Greenberger et al. teaches that adenoviral vectors can deliver active SOD enzymes to cells so as to protect them from damage from free radicals, it must be considered that the ordinary skilled artisan in molecular biology and gene therapy would have been motivated to treat diseases characterized by an excess of free radicals by administering adenoviral vectors capable of expressing a human SOD gene product. It is also noted that since applicants and the prior art agree that excess free radicals cause cellular damage associated with a variety of diseases such as ALS, cardiovascular diseases, etc., the ordinary skilled artisan would have been motivated to reduce the levels of free radicals to treat the disease. This is a common sense approach made obvious by the prior art and applicants admissions as to what the prior art teaches concerning the role of excess free radicals in various disease conditions. Also, applicants' claims read on methods of treating a disease, not curing or preventing the disease and since alleviating one or more symptoms of the disease is treating the

disease, it must be considered that reducing the levels of excess free radicals (which cause cellular damage) would have a palliative effect on the diseases associated with excess free radicals. It is noted that absolute certainty of success in not required, only that the ordinary skilled artisan have a reasonable expectation of success in practicing the claimed invention.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo whose telephone number is (703) 308-1906. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003. The fax phone number for this Group is (703) 308-4242 or (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

David Guzo
October 12, 1999

DAVID GUZO
PRIMARY EXAMINER